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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/667,947	09/22/2000	Stephen James Russell	07039-298001	9619

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	20

DATE MAILED: 07/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/667,947	Applicant(s) Russell et al.
	Examiner Shin-Lin Chen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 23, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *27-43 and 45-58* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *27-43 and 45-58* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some*, c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Upon further consideration of the claimed invention, the finality of the Official action mailed 2-20-03 (Paper No. 15) has been withdrawn.

Applicants' amendment filed 5-23-03 has been entered. Claim 44 has been canceled. Claims 27 and 43 have been amended. Claims 27-43 and 45-58 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 27-43 and 45-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a Measles virus (MV) comprising a nucleic acid, encoding a heterologous marker polypeptide, inserted at the 5' end of viral genes, e.g. N, P, L etc., to monitor gene expression of viral genes, does not reasonably provide enablement for using any Paramyxoviridae virus comprising a nucleic acid, encoding a heterologous marker polypeptide, inserted at the 3' end of viral genes, e.g. N, P, L etc., to monitor gene expression of viral genes in an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 27-42 are directed to a method of monitoring gene expression of viral nucleic acids from virus infected cells within an organism comprising administering to said organism a Paramyxoviridae virus, such as Paramyxovirus, Morbillivirus, Rubulavirus, and Pneumovirus, containing a nucleic acid encoding a heterologous polypeptide, such as CEA, tumor antigen and beta subunit of human choronic gonadotrophin, and detecting the amount of said heterologous polypeptide in said biological fluid, thereby providing an indication of the amount of said gene expression. Claims 28 and 29 specify the heterologous polypeptide is biologically inactive and below 10 kDa, respectively. Claims 33-36 specify the nucleic acid encodes a recombinant fusion protein comprising said heterologous polypeptide fused to an endogenous polypeptide, such as H protein, and a protease cleavage site as an amino acid linker. Claim 37 specifies the Paramyxoviridae virus is replication-competent. Claims 43 and 45-58 are directed to a Paramyxoviridae virus comprising a nucleic acid encoding a heterologous polypeptide as set forth above.

The specification generates Measles Virus (MV) for enhancing fusogenecity by modifying MV F, H, or M protein, recombinant MV expressing single chain antibody (ScAb) against CD38 or CEA on the surface of the virus to alter targeting specificity, and shows co-expression of F protein with chimeric HXL (long linker arm between H protein and scAb) in MC38-CEA cells led to extensive syncytia formation. The two Peng references accompanied with the amendment filed 5-23-03 only disclose putting nucleic acid encoding CEA at the 5' end of endogenous MV viral genes. The claims encompass putting nucleic acid encoding

heterologous polypeptide at any location within the viral genome and detection of said heterologous polypeptide in biological fluid corresponds to gene expression of any viral gene.

The specification fails to provide adequate guidance and evidence for the correlation between the detection of the heterologous polypeptide in a biological fluid and gene expression of any viral gene when the nucleic acid encoding said heterologous polypeptide is located at other than 5' end of viral genes, e.g. in between H and L genes or 3' to the L gene. Although the specification indicates that the expression of Measles virus (MV) is a gradient depending on the distance from the 5' viral promoter (page 26), the specification fails to provide adequate guidance for how the detection or non-detection of the heterologous polypeptide in a biological fluid would correlate to the amount of gene expression of various viral genes. When the nucleic acid encoding the heterologous polypeptide is located at the more distal end from the 5' viral promoter, the expression of said heterologous polypeptide could be insufficient such that said polypeptide can not be detected in a biological fluid and the non-detection of said polypeptide does not correspond to the amount of gene expression of viral genes 5' to the nucleic acid encoding said heterologous polypeptide. Similarly, a mutation that introduces a termination codon or a frameshift mutation 5' to the nucleic acid encoding the heterologous polypeptide would prevent the expression of said heterologous polypeptide but non-detection of said polypeptide does not correspond to the amount of gene expression of viral genes 5' to the nucleic acid encoding said heterologous polypeptide. Further, the specification and Peng references only disclose the use of MV and indicate gradient gene expression of MV genome but the claims

encompass any Paramyxoviridae virus including any virus of various genuses Paramyxovirus, Morbillivirus, Rubulavirus, and Pneumovirus etc. The specification fails to provide adequate guidance and evidence that any virus in the family of Paramyxoviridae would have the same type of gradient gene expression within said viral genome and detection of the heterologous polypeptide in a biological fluid can be used as an indicator for the amount of viral gene expression in a virus infected cells within an organism. Thus, one skilled in the art at the time of the invention would not know how to use the claimed Paramyxoviridae virus to monitor viral gene expression in virus infected cells within an organism.

In addition, claim 45 reads on using nucleic acid encoding heterologous polypeptide having molecular weight that is below 10 kD and said heterologous polypeptide is biologically inactive in an organism. The specification only discloses activation peptides which are released during proteolytic processing zymogens to generate active enzymes and most of those peptides have MW less than 1 kD (bridging pages 15 and 16). The specification fails to provide adequate guidance whether those activation peptides are biologically inactive in an organism. There is no evidence of record that those activation peptides are biologically inactive in an organism such that nucleic acids encoding those activation peptides can be used for the construction of the claimed Paramyxoviridae virus as a marker. Thus, one skilled in the art at the time of the invention would not know how to use the claimed Paramyxoviridae virus comprising nucleic acid encoding heterologous polypeptide having MW less than 10 kD.

Therefore, one skilled in the art at the time of the invention would have to engaged in undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 43, 46-54 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wills, 1992 (US 5,175,099) in view of Schlom et al., 1997 (US 5,698,530).

Claims 43, 46-54 and 58 are directed to a Paramyxoviridae virus, such as a SV40 virus, comprising a nucleic acid sequence encoding a heterologous polypeptide which is a biologically inactive polypeptide, such as a tumor antigen including CEA. Claims 51 and 52 specify the amino linker sequence comprises a protease cleavage site. Claim 53 specifies the Paramyxoviridae virus is replication-competent.

Wills teaches construction of replicable expression vectors, such as retrovirus vector and SV40 vector, comprising a hybrid gene for producing fusion proteins which are secreted in membraneous particles budding from cell membrane in to the culture medium or extracellular space, a process known as retrovirus-mediated secretion, and the hybrid gene contains a proteolytic cleavage site joining a modified retrovirus gag gene and a heterologous gene (e.g. abstract, column 4). Wills also teaches use of membraneous particles for protein purification and in therapeutics (e.g. abstract).

Wills does not teach expressing CEA in a viral vector, such as SV40 vector.

Schlom teaches that CEA is a tumor-associated antigen that has been used clinically as a marker following primary tumor resection and anti-CEA antibodies have been used in diagnostic imaging of primary colon tumors (e.g. column 1). Schlom also teaches construction of a recombinant vaccinia virus or other viral vector expressing CEA protein.

It would have been obvious for one of ordinary skill at the time of the invention to substitute the heterologous gene as taught by Wills with the nucleic acid encoding CEA as taught by Schlom because both the heterologous gene and nucleic acid encoding CEA are DNA

sequences and CEA is heterologous to the retrovirus or SV40 vector and Schlom teaches expressing CEA is a viral vector, i.e. vaccinia vector.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to produce fusion protein comprising CEA that is secreted in membraneous particles by using SV40 vector and purification of said protein and use in therapeutics as taught by Wills with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

S-L Chen